

DOXERCALCIFEROL- doxercalciferol capsule

Heritage Pharmaceuticals Inc. d/b/a Avet Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use doxercalciferol capsules safely and effectively. See full prescribing information for doxercalciferol capsules.

Doxercalciferol capsules, for oral use

Initial U.S. Approval: 1999

INDICATIONS AND USAGE

Doxercalciferol Capsules is a synthetic vitamin D₂ analog:

- Doxercalciferol capsules are indicated for the treatment of secondary hyperparathyroidism in adult patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and adult patients with CKD on dialysis. (1)

DOSAGE AND ADMINISTRATION

- Before initiating treatment, ensure serum calcium is not above the upper limit of normal. (2.1)
- Dosage for doxercalciferol capsules in patients with:
 - Stage 3 or 4 CKD: Initiate dosing at 1 mcg orally once daily. Maximum dose is 3.5 mcg once daily. (2.2)
 - CKD on dialysis: Initiate dosing at 10 mcg orally three times weekly at dialysis (no more frequently than every other day). Maximum dose is 20 mcg three times weekly for a total of 60 mcg weekly. (2.3)
- Target the maintenance dose of doxercalciferol to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits. (2)
- See Full Prescribing Information for dose titration, laboratory monitoring, and important administration instructions. (2)

DOSAGE FORMS AND STRENGTHS

- Capsules: 0.5 mcg, 1 mcg, and 2.5 mcg (3)

CONTRAINDICATIONS

- Hypercalcemia (4)
- Vitamin D toxicity (4)
- Known hypersensitivity to doxercalciferol or any of the inactive ingredients of doxercalciferol capsules (4)

WARNINGS AND PRECAUTIONS

- Hypercalcemia: Can occur during treatment with doxercalciferol and can lead to cardiac arrhythmias and seizures. Severe hypercalcemia may require emergency attention. Risk may be increased when used concomitantly with high dose calcium preparations, thiazide diuretics, or vitamin D compounds. Monitor serum calcium prior to initiation and during treatment and adjust dose accordingly. (2.5.1)
- Digitalis Toxicity: Hypercalcemia increases the risk of digitalis toxicity. In patients using digitalis compounds, monitor serum calcium and patients for signs and symptoms of digitalis toxicity. Increase frequency of monitoring when initiating or adjusting the dose of doxercalciferol. (5.2)
- Serious Hypersensitivity Reactions: Anaphylaxis, with symptoms of angioedema, hypotension, unresponsiveness, chest discomfort, shortness of breath, and cardiopulmonary arrest, has been reported in hemodialysis patients after administration of doxercalciferol. Monitor patients upon treatment initiation for hypersensitivity reactions. Should a reaction occur, discontinue and treat. (5.3)
- Adynamic Bone Disease: May develop and increase risk of fractures if intact PTH levels are suppressed to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust dose if needed. (5.4)

ADVERSE REACTIONS

The most common adverse reactions in patients with Stage 3 or 4 CKD (incidence >5%) were infection, urinary tract infection, chest pain, angina pectoris, constipation, dyspepsia, anemia, leucopenia, dehydration, edema, depression, hypertonia, insomnia, asthenia, paresthesia, cough increased, dyspnea, pruritus, sinusitis, and rhinitis. (6.1)

The most common adverse reactions in patients with CKD on dialysis (incidence >5%) were headache, malaise, edema, nausea/vomiting, dyspnea, dizziness, pruritus, and bradycardia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Avet Pharmaceuticals Inc. at 1-866-901-DRUG (3784) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Cytochrome P450 inhibitors: Formation of the active doxercalciferol moiety may be hindered and may necessitate dosage adjustment. Monitor intact PTH and serum calcium concentrations closely. (7)
- Enzyme inducers: Formation of the active doxercalciferol moiety may be affected and may necessitate dosage

- adjustment. Monitor intact PTH and serum calcium concentrations closely. (7)
- Magnesium-containing products: Combined use may cause hypermagnesemia. Monitor serum magnesium concentrations more frequently and adjust dose as needed. (7)
 - Cholestyramine: May impair absorption of doxercalciferol capsules. Administer doxercalciferol capsules at least 1 hour before or 4 to 6 hours after taking cholestyramine. (7)
 - Mineral oil or other substances that may affect absorption of fat: May impair absorption of doxercalciferol capsules. Administer doxercalciferol capsules at least 1 hour before or 4 to 6 hours after taking substances that may affect absorption.

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- Doxercalciferol capsules are indicated for the treatment of secondary hyperparathyroidism in adult patients with Stage 3 or Stage 4 chronic kidney disease (CKD) and adult patients with CKD on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of Doxercalciferol Capsules

- Ensure serum calcium is not above the upper limit of normal before initiating treatment with doxercalciferol capsules [see *Warnings and Precautions* (5.1)].

2.2 Dosage Recommendations for Doxercalciferol Capsules in Patients with Stage 3 or 4 CKD

- Initiate doxercalciferol capsules at a dose of 1 mcg orally once daily.
- Target the maintenance dose of doxercalciferol to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits.
- Monitor serum calcium, phosphorus, and intact PTH levels at least every two weeks for 3 months after initiation of therapy or dose adjustment, then monthly for 3 months, and every 3 months thereafter.
- Titrate the dose of doxercalciferol capsules based on intact PTH. The dose may be increased at 2-week intervals by 0.5 mcg to achieve the desired therapeutic range of intact PTH. The maximum recommended dose of doxercalciferol capsules is 3.5 mcg administered once daily. Prior to raising the dose, ensure serum calcium is within normal limits.
- Suspend or decrease the dose if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see *Warnings and Precautions* (5.4)] or if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see *Warnings and Precautions* (5.1)]. If suspended, the drug should be restarted after one week at a dose that is at least 0.5 mcg lower.

2.3 Dosage Recommendations for Doxercalciferol Capsules in Patients with CKD on Dialysis

- Initiate doxercalciferol capsules at a dose of 10 mcg orally administered three times weekly at dialysis (no more frequently than every other day).
- Target the maintenance dose of doxercalciferol to intact parathyroid hormone (PTH) levels within the desired therapeutic range and serum calcium within normal limits.
- Monitor serum calcium, phosphorus, and intact PTH levels frequently (e.g., weekly) after initiation of therapy or dose adjustment.
- Titrate the dose of doxercalciferol capsules based on intact PTH. The dose may be increased at 8-week intervals by 2.5 mcg to achieve the desired therapeutic range of intact PTH. The maximum recommended dose of doxercalciferol is 20 mcg administered three times weekly at dialysis for a total dose of 60 mcg weekly. Prior to raising the dose, ensure serum calcium is within normal limits.
- Suspend or decrease the dose if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [see *Warnings and Precautions* (5.4)] or if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [see *Warnings and Precautions* (5.1)]. If suspended, the drug should be restarted one week later at a dose that is at least 2.5 mcg lower.

2.6 Drug Interactions that May Require Dosage Adjustments of Doxercalciferol

- Increased monitoring of serum calcium and dose adjustment of doxercalciferol may be necessary when given concomitantly with drugs that may increase the risk of hypercalcemia [see *Drug Interactions* (7)].
- Increased monitoring of both serum calcium and intact PTH as well as dose adjustment of

doxercalciferol may be necessary when given concomitantly with cytochrome P450 inhibitors or enzyme inducers [see *Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

- 0.5 mcg – White, opaque, oval shaped soft gelatin capsules. Each capsule is imprinted with "HP 538" in black ink.
- 1 mcg – Beige, opaque, oval shaped soft gelatin capsules. Each capsule is imprinted with "HP 539" in black ink.
- 2.5 mcg – Red, opaque, oval shaped soft gelatin capsules. Each capsule is imprinted with "HP 540" in black ink.

4 CONTRAINDICATIONS

Doxercalciferol is contraindicated in patients with:

- Hypercalcemia [see *Warnings and Precautions (5.1)*]
- Vitamin D toxicity [see *Warnings and Precautions (5.1)*]
- Known hypersensitivity to doxercalciferol or any of the inactive ingredients of doxercalciferol capsules; serious hypersensitivity reactions including anaphylaxis and angioedema have been reported [see *Warnings and Precautions (5.3)*, *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia

Hypercalcemia may occur during doxercalciferol treatment. Acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures and may potentiate the effect of digitalis on the heart [see *Warnings and Precautions (5.2)*]. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. Severe hypercalcemia may require emergency attention.

Hypercalcemia may be exacerbated by concomitant administration of high doses of calcium-containing preparations, thiazide diuretics, or other vitamin D compounds [see *Drug Interactions (7)*]. In addition, high intake of calcium and phosphate concomitantly with vitamin D compounds may lead to hypercalciuria and hyperphosphatemia. Patients with a history of hypercalcemia prior to initiating therapy may be at increased risk for development of hypercalcemia with doxercalciferol. In these circumstances, frequent serum calcium monitoring and doxercalciferol dose adjustments may be required.

When initiating doxercalciferol or adjusting doxercalciferol dose, measure serum calcium frequently (weekly in patients with CKD on dialysis or every 2 weeks for patients with stage 3 or 4 CKD). Once a maintenance dose has been established, measure serum calcium monthly for 3 months and then every 3 months. If hypercalcemia occurs, reduce the dose or discontinue doxercalciferol until serum calcium is normal [see *Dosage and Administration (2)*].

Inform patients about the symptoms of elevated calcium (feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss) and instruct them to report new or worsening symptoms when they occur.

5.2 Digitalis Toxicity

Doxercalciferol can cause hypercalcemia [see *Warnings and Precautions (5.1)*] which increases the risk of digitalis toxicity. In patients using doxercalciferol concomitantly with digitalis compounds, monitor both serum calcium and patients for signs and symptoms of digitalis toxicity. Increase the frequency of monitoring when initiating or adjusting the dose of doxercalciferol [see *Drug Interactions (7)*].

5.3 Serious Hypersensitivity Reactions

Hypersensitivity reactions include anaphylaxis with symptoms of angioedema (involving face, lips, tongue and airways), hypotension, unresponsiveness, chest discomfort, shortness of breath, and cardiopulmonary arrest. These reactions may occur separately or together.

Monitor patients receiving doxercalciferol upon initiation of treatment for hypersensitivity reactions. Should a hypersensitivity reaction occur, discontinue doxercalciferol, monitor and treat if indicated [see *Contraindications (4)*].

5.4 Adynamic Bone Disease

Adynamic bone disease with subsequent increased risk of fractures may develop if intact PTH levels are suppressed by doxercalciferol to abnormally low levels. Monitor intact PTH levels to avoid oversuppression and adjust the doxercalciferol dose, if needed [see *Dosage and Administration (2)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

- Hypercalcemia [see *Warnings and Precautions (5.1)*]
- Serious Hypersensitivity Reactions [see *Warnings and Precautions (5.3)*]
- Adynamic Bone Disease [see *Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions in patients with stage 3 or 4 CKD

Doxercalciferol capsules have been evaluated in two placebo-controlled, double-blind 24 week studies in patients with Stage 3 or 4 CKD. Patients were treated with doxercalciferol capsules (n=27) or placebo (n=28) [see *Clinical Studies (14.1)*]. Adverse reactions occurring in the doxercalciferol capsules group at a frequency of 5% or greater and more frequently than in the placebo group are presented in Table 1.

Table 1: Adverse Reactions Occurring in $\geq 5\%$ Doxercalciferol Capsule-Treated Patients with CKD on Predialysis and Greater than Placebo in Two Double-Blind Clinical Studies

Adverse Reaction*	Doxercalciferol (n=27) %	Placebo (n=28) %
Infection/bacterial infection/viral infection	30	25
Constipation	26	11
Rhinitis	22	11
Anemia	19	4
Cough	19	4
Dyspnea	19	11
Paresthesia	15	11
Asthenia	15	11
Insomnia	15	4
Hypertonia	11	4
Angina pectoris	8	0
Dehydration	7	4
Depression	7	0

Dyspepsia	7	4
Edema	7	4
Urinary tract infection	7	4
Leukopenia	7	0
Chest pain	7	4
Pruritus	7	4
Sinusitis	7	4

* Pooled data on adverse reactions from clinical study reports (Studies BCI-CH-115 and BCI-CH-119).

Adverse reactions in patients with CKD on dialysis

Doxercalciferol capsules have been evaluated in two placebo-controlled, double-blind studies in patients with CKD on hemodialysis. Patients were treated with doxercalciferol capsules (n=61) or placebo (n=61) [see *Clinical Studies* (14.2)]. After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, all patients received doxercalciferol capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either doxercalciferol capsules or placebo. Adverse reactions occurring in the doxercalciferol capsule groups at a frequency of 2% or greater, and more frequently than in the placebo group are presented in Table 2.

Table 2: Adverse Reactions Occurring in $\geq 2\%$ Doxercalciferol Capsule-Treated Patients with CKD on Dialysis and Greater than Placebo in Two Double-Blind Clinical Studies

Adverse Reaction*	Doxercalciferol (n=61) %	Placebo (n=61) %
Edema	34	21
Malaise	28	20
Headache	28	18
Nausea/Vomiting	21	20
Dizziness	12	10
Dyspnea	12	7
Pruritus	8	7
Bradycardia	7	5
Anorexia	5	3
Dyspepsia	5	2
Arthralgia	5	0
Weight increase	5	0
Abscess	3	0
Sleep disorder	3	0

* A patient who reported the same medical term more than once was counted only once for that medical term.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of doxercalciferol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or to establish a causal relationship to drug exposure.

Hypersensitivity reactions include anaphylaxis with symptoms of angioedema (involving face, lips, tongue and airways), hypotension, unresponsiveness, chest discomfort, shortness of breath, cardiopulmonary arrest, pruritus, and skin burning sensation.

7 DRUG INTERACTIONS

Tables 3 and 4 include clinically significant drug interactions with doxercalciferol.

Table 3: Clinically Significant Drug Interactions with Doxercalciferol Capsules

Drugs that May Increase the Risk of Hypercalcemia	
<i>Clinical Impact</i>	Concomitant administration of high doses of calcium-containing preparations or other vitamin D compounds may increase the risk of hypercalcemia. Thiazide diuretics are known to induce hypercalcemia by reducing excretion of calcium in the urine.
<i>Examples</i>	Calcium-containing products, other vitamin D compounds or thiazide diuretics
<i>Intervention</i>	Monitor serum calcium concentrations more frequently and adjust doxercalciferol dose as needed [see <i>Warnings and Precautions (5.1)</i>].
Digitalis Compounds	
<i>Clinical Impact</i>	Doxercalciferol can cause hypercalcemia which can potentiate the risk of digitalis toxicity.
<i>Intervention</i>	Monitor patients for signs and symptoms of digitalis toxicity and increase frequency of serum calcium monitoring when initiating or adjusting the dose of doxercalciferol in patients receiving digitalis compounds [see <i>Warnings and Precautions (5.2)</i>].
Cytochrome P450 Inhibitors	
<i>Clinical Impact</i>	Doxercalciferol is activated by CYP 27 in the liver. Cytochrome P450 inhibitors may inhibit the 25-hydroxylation of doxercalciferol and thus reduce the formation of active doxercalciferol moiety [see <i>Clinical Pharmacology (12.3)</i>].
<i>Examples</i>	Ketoconazole and erythromycin
<i>Intervention</i>	If a patient initiates or discontinues therapy with a cytochrome P450 inhibitor, dose adjustment of doxercalciferol may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Enzyme Inducers	
<i>Clinical Impact</i>	Doxercalciferol is activated by CYP 27 in the liver. Enzyme inducers may affect the 25-hydroxylation of doxercalciferol [see <i>Clinical Pharmacology (12.3)</i>].
<i>Examples</i>	Glutethimide and phenobarbital
<i>Intervention</i>	If a patient initiates or discontinues therapy with an enzyme inducer, dose adjustment of doxercalciferol may be necessary. Monitor intact PTH and serum calcium concentrations closely.
Magnesium-containing Products	
<i>Clinical Impact</i>	Concomitant administration of doxercalciferol and high doses of magnesium-containing products may increase the risk of hypermagnesemia.
<i>Examples</i>	Magnesium-containing products such as antacids
<i>Intervention</i>	Avoid use of magnesium-containing products and doxercalciferol in patients on chronic renal dialysis.

Table 4: Clinically Significant Drug Interactions with Doxercalciferol Capsules

Cholestyramine	
<i>Clinical Impact</i>	Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins. Therefore, it may impair intestinal absorption of doxercalciferol capsules.
<i>Intervention</i>	Administer doxercalciferol capsules at least 1 hour before or 4 to 6 hours after taking cholestyramine.
Mineral Oil or other Substances that May Affect Absorption of Fat	
<i>Clinical Impact</i>	The use of mineral oil or other substances that may affect absorption of fat may influence the absorption and availability of doxercalciferol.

<i>Intervention</i>	Administer doxercalciferol capsules at least 1 hour before or 4 to 6 hours after taking mineral oil or other substances that may affect absorption of fat.
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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The limited available data with doxercalciferol in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with chronic kidney disease in pregnancy [see *Clinical Considerations*]. In reproduction studies in rats and rabbits administered doxercalciferol during organogenesis at up to 20 mcg/kg/day and 0.1 mcg/kg/day, respectively (approximately 25 times (rats) and less than (rabbits) the maximum recommended human oral dose of 60 mcg/week based on mcg/m² body surface area), no adverse developmental effects were observed [see *Data*].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Chronic kidney disease in pregnancy increases the risk for maternal hypertension and preeclampsia, miscarriage, preterm delivery polyhydramnios, stillbirth, and low-birth-weight infants.

Data

Animal data

There were no adverse effects on fetal development when doxercalciferol was administered at doses up to 20 mcg/kg/day in pregnant rats or doses up to 0.1 mcg/kg/day in pregnant rabbits during the period of organogenesis.

8.2 Lactation

Risk Summary

There is no information available on the presence of doxercalciferol in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Infants exposed to doxercalciferol through breast milk should be monitored for signs and symptoms of hypercalcemia [see *Clinical Considerations*].

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for doxercalciferol and any potential adverse effects on the breastfed child from doxercalciferol or from the underlying maternal condition.

Clinical Considerations

Monitoring of serum calcium in the infant should be considered.

8.4 Pediatric Use

Safety and efficacy of doxercalciferol in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of doxercalciferol did not include sufficient numbers of patients 65 years or over to determine whether they respond differently from younger subjects. In general, dose selection for an

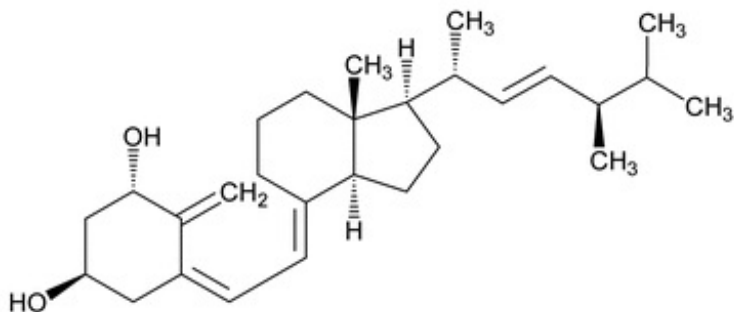
8.6 Hepatic Impairment

10 OVERDOSAGE

Based on similarities between doxercalciferol and its active metabolite, $1\alpha,25\text{-(OH)}_2\text{D}_2$, it is expected that doxercalciferol is not removed from the blood by dialysis.

11 DESCRIPTION

Doxercalciferol is a colorless crystalline compound with a calculated molecular weight of 412.66 and a molecular formula of $C_{28}H_{44}O_2$. It is soluble in oils and organic solvents, but is relatively insoluble in water. Chemically, doxercalciferol is (1 α ,3 β ,5Z,7E,22E)-9,10-secoergosta-5,7,10(19),22-tetraene-1,3-diol. The structural formula is:



Doxercalciferol capsules are soft gelatin capsules containing 0.5 mcg, 1 mcg, or 2.5 mcg doxercalciferol for oral use. Each capsule also contains butylated hydroxyanisole (BHA), ethanol, and medium-chain triglycerides. The capsule shells contain gelatin, glycerin, iron oxide black and titanium dioxide. In addition, the 0.5 mcg capsule shells contain shellac glaze, the 1 mcg capsule shells contain FD&C Blue No. 1, FD&C Yellow No. 6, shellac and the 2.5 mcg capsule shells contain FD&C Red No. 40 and shellac.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxercalciferol is a synthetic vitamin D₂ analog that requires metabolic activation to form the active 1 α ,25-(OH)₂D₂ metabolite, which binds to the vitamin D receptor (VDR) to result in the selective

activation of vitamin D responsive pathways. Vitamin D and doxercalciferol have been shown to reduce PTH levels by inhibiting PTH synthesis and secretion.

12.3 Pharmacokinetics

Absorption

In healthy volunteers, peak blood levels of $1\alpha,25\text{-(OH)}_2\text{D}_2$, the major metabolite of doxercalciferol, are attained at 8 hours after a single intravenous dose of doxercalciferol and at 11 to 12 hours following capsule doses.

Elimination

The mean elimination half-life of $1\alpha,25\text{-(OH)}_2\text{D}_2$ after an oral dose is approximately 32 to 37 hours with a range of up to 96 hours.

Metabolism

Doxercalciferol is activated by CYP 27 in the liver to form $1\alpha,25\text{-(OH)}_2\text{D}_2$ (major metabolite) and $1\alpha,24\text{-dihydroxyvitamin D}_2$ (minor metabolite). Activation of doxercalciferol does not require the involvement of the kidneys.

Specific Populations

Patients with renal impairment

The mean elimination half-life of $1\alpha,25\text{-(OH)}_2\text{D}_2$ in patients with end-stage renal disease (ESRD) and in healthy volunteers appears to be similar following an oral dose. Hemodialysis causes a temporary increase in $1\alpha,25\text{-(OH)}_2\text{D}_2$ mean concentrations, presumably due to volume contraction. $1\alpha,25\text{-(OH)}_2\text{D}_2$ is not removed from blood during hemodialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 104-week carcinogenicity study in rats, there was an increased incidence of benign and malignant adrenal pheochromocytomas in both males and females at oral doses of 0.04, 0.13, and 0.39 mcg/kg/day (less than the maximum recommended human oral dose of 60 mcg/week based on mcg/m² body surface area). This increased incidence of pheochromocytomas in rats may be due to altered calcium homeostasis by doxercalciferol. No evidence of genetic toxicity was observed in an *in vitro* bacterial mutagenicity assay (Ames test) or a mouse lymphoma gene mutation assay. Doxercalciferol caused structural chromatid and chromosome aberrations in an *in vitro* human lymphocyte clastogenicity assay with metabolic activation. However, doxercalciferol was negative in an *in vivo* mouse micronucleus clastogenicity assay.

Doxercalciferol had no effect on male or female fertility in rats at oral doses up to 2.5 mcg/kg/day (approximately 3 times the maximum recommended human oral dose of 60 mcg/week based on mcg/m² body surface area).

14 CLINICAL STUDIES

14.1 Clinical Studies of Doxercalciferol Capsules in Patients with Stage 3 or 4 CKD

The safety and effectiveness of doxercalciferol capsules were evaluated in two clinical studies in 55 patients with Stage 3 or 4 CKD. Eighty-two percent of the patients were male, the average age was 65 years, 51% were Caucasian, 40% African-American, and the average serum intact PTH level at baseline was 195 pg/mL. While levels of 25-(OH) vitamin D were not evaluated at baseline, retrospective assessments of stored serum revealed that the mean \pm SD serum 25-(OH) vitamin D was 19 ± 8 ng/mL (range: <5 to 54 ng/mL) in the study population.

After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, one group received doxercalciferol capsules and the other placebo during the double-blind period of 24 weeks. The initial dose of doxercalciferol capsules was 1 mcg per day. The dosage of doxercalciferol capsules was adjusted as necessary by the investigator to reduce intact PTH levels to a target of $\geq 30\%$ below post-washout baseline. The maximum dosage was limited to 3.5 mcg per day. If at any time during the trial intact PTH fell below 15 pg/mL, doxercalciferol capsules were immediately suspended and restarted at a lower dosage the following week.

Decreases in the mean plasma intact PTH from baseline values were calculated using as baseline the average of the last 2 values obtained during the 8-week washout phase. In analyses of pooled data from the two studies, intact PTH levels decreased from baseline by an average of 101 pg/mL in the doxercalciferol capsules group and by 4 pg/mL in the placebo group ($p < 0.001$). Twenty (74%) of 27 subjects in the doxercalciferol capsules group achieved mean plasma intact PTH suppression of $\geq 30\%$ from baseline for the last four weeks of treatment, whereas two (7%) of the 28 subjects treated with placebo achieved this level of intact PTH suppression.

14.2 Clinical Studies of Doxercalciferol Capsules in Patients with CKD on Dialysis

The safety and effectiveness of doxercalciferol capsules were evaluated in two double-blind, placebo-controlled, multicenter clinical studies (Study A and Study B) in a total of 138 patients with CKD on hemodialysis. Patients in Study A were an average age of 52 years (range: 22 to 75), were 55% male, and were 58% African-American, 31% Caucasian, and 11% Hispanic, and had been on hemodialysis for an average of 53 months. Patients in Study B were an average of 52 years (range: 27 to 75), were 45% male, and 99% African-American, and 1% Caucasian, and had been on hemodialysis for an average of 56 months. After randomization to two groups, eligible patients underwent an 8-week washout period during which no vitamin D derivatives were administered to either group. Subsequently, all patients received doxercalciferol capsules in an open-label fashion for 16 weeks followed by a double-blind period of 8 weeks during which patients received either doxercalciferol capsules or placebo. The initial dose of doxercalciferol capsules during the open-label phase was 10 mcg after each dialysis session (3 times weekly) for a total of 30 mcg per week. The dosage of doxercalciferol was adjusted as necessary by the investigator to achieve intact PTH levels within 150 pg/mL to 300 pg/mL. The maximum dosage was limited to 20 mcg after each dialysis session (60 mcg/week). If at any time during the trial intact PTH fell below 150 pg/mL, Doxercalciferol was immediately suspended and restarted at a lower dosage the following week. Mean weekly doses during the 16-week open-label period ranged from 15 mcg to 29 mcg in Study A and from 19 mcg to 28 mcg in Study B.

One hundred and six (77%) of the 138 patients who were treated with doxercalciferol capsules during the 16-week open-label phase achieved intact PTH levels ≤ 300 pg/mL. Ninety-four (68%) of these patients exhibited plasma intact PTH levels ≤ 300 pg/mL on at least 3 occasions. Eighty-seven (63%) patients had plasma intact PTH levels < 150 pg/mL on at least one occasion during the open-label phase of study participation.

Decreases in plasma intact PTH from baseline values were calculated using as baseline the average of the last 3 values obtained during the 8-week washout phase and are displayed in Table 5.

Table 5: Intact PTH Summary Data for Patients with CKD on Dialysis Receiving Doxercalciferol Capsules in Studies A and B

		Intact PTH (pg/mL)	
		means \pm SD (n)*	
		p-value vs Baseline	
		p-value vs Placebo	
		Doxercalciferol Capsules	Placebo
Study A	Baseline	797.2 \pm 443.8 (30)	847.1 \pm 765.5 (32)

		NA 0.97	— —
	Week 16 (open-label)	384.3 ± 397.8 (24) <0.001 0.72	526.5 ± 872.2 (29) <0.001 —
	Week 24 (double-blind)	404.4 ± 262.9 (21) <0.001 0.008	672.6 ± 356.9 (24) 0.70 —
Study B	Baseline	973.9 ± 567.0 (41) NA 0.81	990.4 ± 488.3 (35) — —
	Week 16 (open-label)	476.1 ± 444.5 (37) <0.001 0.91	485.9 ± 443.4 (32) <0.001 —
	Week 24 (double-blind)	459.8 ± 443.0 (35) <0.001 <0.001	871.9 ± 623.6 (30) <0.065 —

* All subjects; last value carried to discontinuation.

NA = not applicable

Doxercalciferol capsules treatment resulted in a statistically significant reduction from baseline in mean intact PTH levels during the 16-week open-label treatment period in more than 94% of the 138 treated patients. During the double-blind period (weeks 17 to 24), the reduction in mean intact PTH levels was maintained in the doxercalciferol capsules treatment group compared to a return to near baseline in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Doxercalciferol capsules are oval, soft gelatin capsules supplied as follows.

Strength	Capsule Color	Imprint Code	Package Size	NDC
0.5 mcg	White, Opaque	HP 538	Bottle of 50 capsules	23155-538-25
1 mcg	Beige, Opaque	HP 539	Bottle of 50 capsules	23155-539-25
2.5 mcg	Red, Opaque	HP 540	Bottle of 50 capsules	23155-540-25

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F)

[see USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

Hypercalcemia

Advise patients to contact a health care provider if they develop symptoms of elevated calcium (e.g. feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss) [see Warnings and Precautions (5.1)].

Hypersensitivity

Inform patients that hypersensitivity reactions can occur with doxercalciferol [see Warnings and Precautions (5.3)].

Monitoring

Inform patients that they will need routine monitoring of laboratory parameters such as calcium and intact PTH while receiving doxercalciferol. Inform patients that more frequent monitoring is necessary during the initiation of therapy, following dose changes or when potentially interacting medications are started or discontinued [see *Dosage and Administration* (2), *Drug Interactions* (7)].

Drug Interactions

Advise patients to inform their physician of all medications, including prescription and nonprescription drugs, and supplements they are taking. Advise patients to also inform their physician that they are receiving doxercalciferol if a new medication is prescribed [see *Drug Interactions* (7)].

Distributed by:

Avet Pharmaceuticals Inc.

East Brunswick, NJ 08816

1.866.901.DRUG (3784)



51U000000118US03

Revised: 10/2019

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL 0.5 mcg

NDC 23155-538-25

Doxercalciferol Capsules

0.5 mcg

50 Capsules

Rx only

The image shows a simulated principal display panel for a box of Doxercalciferol Capsules. The panel is divided into several sections. On the left, it displays the NDC number 23155-538-25, the product name "Doxercalciferol Capsules", the strength "0.5 mcg", and "50 Capsules Rx only". Below this is the Avet Pharma logo. The central section contains important usage instructions: "Each capsule contains: Doxercalciferol...0.5 mcg", "Usual Dosage: See package insert for complete prescribing information.", "Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature.]", and a warning to "KEEP THIS AND ALL THE DRUGS OUT OF THE REACH OF CHILDREN." It also lists the distributor: "Avet Pharmaceuticals Inc., East Brunswick, NJ 08816", the toll-free number "1.866.901.DRUG (3784)", the NDC number "51U000000115US03", and the revision date "Rev. 10/2019". On the right side of the panel is a barcode with the number "23155-538-25" printed below it. The far right section of the panel has the text "No Varnish" printed vertically.

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL 1 mcg

NDC 23155-539-25

Doxercalciferol Capsules

1 mcg

50 Capsules

Rx only

NDC 23155-539-25

Doxercalciferol Capsules

1 mcg

50 Capsules Rx only



Each capsule contains:
Doxercalciferol...1 mcg

Usual Dosage: See package insert for complete prescribing information.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature.]

KEEP THIS AND ALL THE DRUGS OUT OF THE REACH OF CHILDREN.

Distributed by:
Avet Pharmaceuticals Inc.
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51U000000116US03
Rev. 10/2019


N 3 23155-539-25 7

No Varnish

PACKAGE LABEL.PRINCIPAL DISPLAY PANEL 2.5 mcg

NDC 23155-540-25

Doxercalciferol Capsules

2.5 mcg

50 Capsules

Rx only

NDC 23155-540-25

Doxercalciferol Capsules

2.5 mcg

50 Capsules Rx only



Each capsule contains:
Doxercalciferol...2.5 mcg

Usual Dosage: See package insert for complete prescribing information.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature.]

KEEP THIS AND ALL THE DRUGS OUT OF THE REACH OF CHILDREN.

Distributed by:
Avet Pharmaceuticals Inc.
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51U000000117US03
Rev. 10/2019


N 3 23155-540-25 3

No Varnish

DOXERCALCIFEROL

doxercalciferol capsule

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:23155-538
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
DOXERCALCIFEROL (UNII: 3DIZ9LF5Y9) (DOXERCALCIFEROL - UNII:3DIZ9LF5Y9)		DOXERCALCIFEROL	0.5 ug
Inactive Ingredients			
Ingredient Name			Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)			
ALCOHOL (UNII: 3K9958V90M)			

MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)				
GELATIN (UNII: 2G86QN327L)				
GLYCERIN (UNII: PDC6A3C0OX)				
FERROSO FERRIC OXIDE (UNII: XM0M87F357)				
SHELLAC (UNII: 46N107B71O)				
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)				
Product Characteristics				
Color	WHITE (WHITE)		Score	no score
Shape	OVAL		Size	8mm
Flavor			Imprint Code	HP538
Contains				
Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:23155-538-25	50 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2020	
Marketing Information				
Marketing Category		Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA		ANDA205360	10/31/2020	

DOXERCALCIFEROL			
doxercalciferol capsule			
Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:23155-539
Route of Administration	ORAL		
Active Ingredient/Active Moiety			
Ingredient Name		Basis of Strength	Strength
DO XERCALCIFEROL (UNII: 3DIZ9LF5Y9) (DO XERCALCIFEROL - UNII:3DIZ9LF5Y9)		DOXERCALCIFEROL	1 ug
Inactive Ingredients			
Ingredient Name			Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)			
ALCOHOL (UNII: 3K9958V90M)			
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)			
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)			
FERROSO FERRIC OXIDE (UNII: XM0M87F357)			
GLYCERIN (UNII: PDC6A3C0OX)			

GELATIN (UNII: 2G86QN327L)	
SHELLAC (UNII: 46N107B71O)	
FD&C BLUE NO. 1 (UNII: H3R47K3TBD)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	

Product Characteristics

Color	BROWN (BEIGE)	Score	no score
Shape	OVAL	Size	8mm
Flavor		Imprint Code	HP539
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:23155-539-25	50 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205360	10/31/2020	

DOXERCALCIFEROL

doxercalciferol capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:23155-540
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DOXERCALCIFEROL (UNII: 3DIZ9LF5Y9) (DOXERCALCIFEROL - UNII:3DIZ9LF5Y9)	DOXERCALCIFEROL	2.5 ug

Inactive Ingredients

Ingredient Name	Strength
BUTYLATED HYDROXYANISOLE (UNII: REK4960K2U)	
ALCOHOL (UNII: 3K9958V90M)	
MEDIUM-CHAIN TRIGLYCERIDES (UNII: C9H2L21V7U)	
GELATIN (UNII: 2G86QN327L)	
GLYCERIN (UNII: PDC6A3C0OX)	
FERROSO FERRIC OXIDE (UNII: XM0M87F357)	
SHELLAC (UNII: 46N107B71O)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	

Product Characteristics

Color	RED (RED)	Score	no score
Shape	OVAL	Size	8 mm
Flavor		Imprint Code	HP540
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:23155-540-25	50 in 1 BOTTLE; Type 0: Not a Combination Product	10/31/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA205360	10/31/2020	

Labeler - Heritage Pharmaceuticals Inc. d/b/a Avet Pharmaceuticals Inc. (780779901)

Establishment

Name	Address	ID/FEI	Business Operations
Heritage Pharma Labs Inc. d/b/a Avet Pharmaceuticals Labs Inc.		189630168	ANALYSIS(23155-538, 23155-539, 23155-540) , LABEL(23155-538, 23155-539, 23155-540) , MANUFACTURE(23155-538, 23155-539, 23155-540) , PACK(23155-538, 23155-539, 23155-540)

Revised: 9/2020

Heritage Pharmaceuticals Inc. d/b/a Avet Pharmaceuticals Inc.